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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/067,449	02/05/2002	Gunter Muller	DEAV2001/0002	7390

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EXAMINER

DUNSTON, JENNIFER ANN

ART UNIT	PAPER NUMBER
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1636

DATE MAILED: 05/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

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Office Action Summary**Application No.**

10/067,449

Applicant(s)

MULLER ET AL.

Examiner

Jennifer Dunston

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 03 May 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-25 is/are pending in the application.
- 4a) Of the above claim(s) 11-25 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-10 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|--|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input checked="" type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. <u>05/12/04</u> . |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>4/24/03, 6/24/03</u> . | 6) <input type="checkbox"/> Other: _____. |

DETAILED ACTION

Receipt is acknowledged of an amendment, filed 5/5/2004, in which several claims were amended (claims 2-11, 13-17, 19-25) and foreign priority was claimed under 35 U.S.C. § 119.

Receipt is also acknowledged of applicant's election of Group I (claims 1-10) in Paper No. 2367. Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). A mere broad allegation that the requirement to restrict is in error, in that claims 18 and 19 also belong to Group I, does not comply with 37 C.F.R. § 1.111. It is noted that applicants do not provide a rational for their assertion that claims 18 and 19 belong in Group I. It is further noted that although claim 19 recites that claims 18-19 are drawn to strains of *Saccharomyces cerevisiae* which can no longer grow on substrates with hexoses as the sole carbon source and whose ability to grow on hexoses as a sole carbon source is restored with a **Glut4** gene, it appears from reading the specification that the claims are actually directed to strains where the ability to grow on a hexose is restored upon expression of a Glut1 gene (see table 1 for DSM 14026 and DSM 14027 of claim 18; SEQ ID No. 13 or 14) expressed in the strain, and methods of making such strains.

Applicant's representative, F. Aaron Dubberley, was contacted by telephone on 5/12/04. Mr. Dubberley confirmed that the request to include claims 18-19 in Group I was made in error. Further, Mr. Dubberley affirmed election of Group I (claims 1-10).

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Claims 1-25 are pending in the instant application. Of these, claims 11-25 are withdrawn from consideration as being directed to non-elected inventions.

Oath/Declaration

Receipt of a properly executed Oath/Declaration, filed 7/8/02, is acknowledged.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-6, and 8-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 is drawn to yeast strains which can no longer grow on substrates with hexoses as the sole carbon source and whose ability to grow on a hexose can be restored when a Glut4 gene is expressed in the strain. Claim 8 recites a step of providing such a strain. The yeast strains must contain a mutation or combination of mutations that make the yeast strain unable to grow in the presence of hexoses as the sole carbon source in such a manner as to allow complementation by expression of a Glut4 transporter.

The rejected claim thus comprises a set of yeast strains with a genetic background that can be derived from any mutagenesis procedure resulting in any type of mutation, such as insertion, deletion, transition, transversion or gross rearrangement of the yeast genome. Mutations are not limited to known transporter genes. The mutations required for functional expression of a Glut4 transporter may include mutations that affect the trafficking of transmembrane proteins to the cell surface or that affect the respiratory capacity of the yeast, for example. Functionally, the yeast strain must not grow on hexoses as the sole carbon source; however, growth must be restored by the functional expression of a Glut4 transporter. Thus, the rejected claims encompass an enormous genus of yeast strains that must meet very specific functional limitations.

The instant specification describes a known yeast strain in which all of the transporters which are capable of taking up hexoses have been removed by deletion (Wieczorke et al., FEBS Lett. 464, 123-128, 1999). Wieczorke et al. teach that this strain is not capable of growing on a substrate with glucose as the sole carbon source. The instant specification teaches that this yeast strain requires further modification to allow for significant glucose transport into the yeast by a Glut4 transporter (e.g. page 4, lines 4-6; page 23, lines 10-29). Yeast strains expressing Glut4 from a plasmid vector carrying a Glut4 gene under the control of a yeast promoter are transformed into the yeast, and yeast cells containing mutation(s) are identified by growth on a substrate with glucose as the sole carbon source. There is no description in the specification as originally filed of the mutations that meet the claim limitations. For example, strains

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DSM 14038, DSM 14039 and DSM 14040 listed in table 1 contain unspecified mutation(s) that allow for complementation of the growth phenotype by a Glut4 transporter. It is not possible from reading the examples to envision what types of mutations have been introduced, how many mutations have been introduced in each yeast strain or which genes have incurred mutations.

Even if one accepts that the examples described in the specification meet the claim limitations of the rejected claim with regard to structure and function, the examples are only representative of a few yeast strains within the broad genus of yeast strains embraced by the rejected claims that actually meet the functional limitations of the claims. The results described are not predictive of the mutation, or combination of mutations, required for the generation of a yeast strain that cannot grow on a hexose as a sole carbon source, where complementation of this phenotype can be achieved by expression of a Glut4 gene. It is impossible for one to extrapolate from the few uncharacterized yeast strains described herein those yeast strains that would necessarily meet the structural/ functional characteristics of the rejected claims.

Therefore, there is no structural/functional basis provided by the prior art or instant specification for one of skill in the art to envision those mutations or combination of mutations that 1) prevent the growth of a given strain of *Saccharomyces cerevisiae* on hexoses as a sole carbon source and 2) allow complementation of the growth phenotype by expression of a Glut4 gene under the control of a yeast promoter. Therefore, one of skill in the art would not have been able to envision a representative number of specific mutations or combination of mutations sufficient to describe the

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broad genus of yeast strains encompassed by the rejected claims. One of skill in the art would thus have reasonably concluded the applicant was not in possession of the claimed invention.

Claims 2 and 7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 2 and 7 are drawn to or encompass the strains of *Saccharomyces cerevisiae* deposited as DSM 14035, DSM 14036, DSM 14037, DSM 14038, DSM 14039 and DSM 14040.

The application discloses strains of *Saccharomyces cerevisiae* that are encompassed by the definitions for **biological material** set forth in 37 C.F.R. § 1.801. Because it is apparent that this biological material is essential for practicing the claimed invention, it must be obtainable by a reproducible method set forth in the specification or otherwise be known and readily available to the public as detailed in 37 C.F.R. §§ 1.801 through 1.809.

It is unclear whether this biological material is known and readily available to the public or that the written instructions are sufficient to reproducibly construct this biological material from starting materials known and readily available to the public.

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Accordingly, availability of such biological material is deemed necessary to satisfy the enablement provisions of 35 U.S.C. § 112. If this biological material is not obtainable or available, the requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the biological material. In order for a deposit to meet all criteria set forth in 37 C.F.R. §§ 1.801-1.809, applicants or assignee must provide assurance of compliance with provisions of 37 C.F.R. §§ 1.801-1.809, in the form of a declaration or applicant's representative must provide a statement. The content of such a declaration or statement is suggested by the enclosed attachment. Because such deposit will not have been made prior to the effective filing date of the instant application, applicant is required to submit a verified statement from a person in a position to corroborate the fact, which states that the biological material which has been deposited is the biological material specifically identified in the application as filed (37 C.F.R. § 1.804). Such a statement need not be verified if the person is an agent or attorney registered to practice before the Office. It is noted that the Applicant has deposited the yeast strains at the Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH (DSMZ). However, Applicant is also reminded that the specification must contain reference to the deposit, date of deposit, and name and address of the depository. A statement that all restrictions on the availability to the public of the material so deposited will be irrevocably removed upon granting of a patent is also required.

Claim 3 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabled for embodiments where the strain of part (b) is subjected to random mutagenesis followed by subsequent screening of mutagenized cells to identify cells able to grow on a hexose as a sole carbon source upon expression of a Glut4 transporter, does not reasonably provide enablement for successful complementation of the growth phenotype by expression of Glut4 without mutagenesis and subsequent screening of the yeast strain. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The nature of the invention is relatively complex. The invention requires a strain of *Saccharomyces cerevisiae* which can no longer grow on substrates with hexoses as the only carbon source. Complementation of this phenotype must be achieved by functional expression of a mammalian transporter (i.e. Glut4 transporter) in the yeast cell. Heterologous expression of a functional Glut4 transporter requires a number of different cellular factors to allow complementation to occur (e.g. proper processing and trafficking to the plasma membrane).

Breadth of the claims: The claim encompasses mutations that eliminate the function of all hexose transporters of the yeast strain. Moreover, the claim broadly encompasses additional mutations that are uncharacterized (see below).

Guidance of the specification and existence of working examples: The specification teaches that the transformation of a yeast strain, in which all of the transporters that are capable of taking up hexoses have been removed by deletion, with an expression vector which carries a Glut4 gene under the control of a yeast promoter is not sufficient by itself to obtain complementation of the growth phenotype on minimal media comprising a hexose as the sole carbon source (e.g. page 4, lines 2-6; page 22-23). The specification teaches that the yeast strain requires additional modifications to allow functional expression of the Glut4 transporter (e.g. page 4, lines 2-6). In the working examples, functional expression of Glut4 could not be achieved merely by screening for natural mutants of step (b) and required the additional step of U.V. mutagenesis (page 23, lines 15-29). Subsequent selection of a mutagenized yeast strain (EBY.SY) transformed with a vector which carries a Glut4 gene under the control of a yeast promoter resulted in strains capable of functional expression of Glut4 (page 25, lines 8-30).

State of the art: Kasahara et al. (Biochemica et Biophysica Acta, 1997) teach expression of a Glut4 transporter in a strain of *Saccharomyces cerevisiae* in which two genes involved in glucose transport, HXT2 and SNF3, were disrupted. Although Glut4 transporter protein was produced by the yeast cells, it was retained in an intracellular

compartment and was not transferred to the cell surface, resulting in the absence of glucose transport in whole cells (page 114, results section).

Predictability of the art: The teachings of the prior art and specification show the unpredictable nature of practicing the claimed method without further random mutagenesis and subsequent screening of mutagenized cells expressing Glut4.

Amount of experimentation necessary: Given the combination of the above factors, it would have required undue, unpredictable experimentation to practice the full, broad scope of the claimed method.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: any step where the strain of step (b) has undergone further random mutagenesis followed by a step of selection on a substrate with hexoses as the sole carbon source while expressing Glut4. The instant specification teaches that for such a strain of yeast comprising a Glut4 expression vector, "functional expression of Glut4 requires further adaptations of this yeast strain."

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(page 4, lines 2-6). In the working examples, it is demonstrated that only after random mutagenesis of the strain lacking hexose transporters was the ability to grow on hexose upon expression of Glut4 obtained (e.g. pages 22-23). Therefore, it would be remedial to amend claim 3 to include language reciting that the strain obtained in step (b) is subject to random mutagenesis and subsequent screening for restored ability to grow on a hexose as a sole carbon source while expressing Glut4.

Conclusion

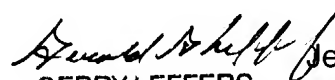
No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


GERRY LEFFERS
PRIMARY EXAMINER

Jennifer Dunston
Examiner
Art Unit 1636

jad